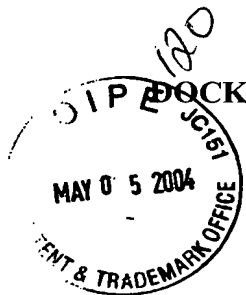


05/06/04

IFW AF/1635



POCKET NO.: ISIS-4943

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Phillip Dan Cook and Andrew Kawasaki

Confirmation No.: 3783

Application No.: 09/996,263

Group Art Unit: 1635

Filing Date: November 28, 2001

Examiner: James Schultz

For: SUGAR MODIFIED OLIGONUCLEOTIDES

EXPRESS MAIL LABEL NO: EL 998516802 US
DATE OF DEPOSIT: May 5, 2004

EL998516802US

MS Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**REVISED APPEAL BRIEF TRANSMITTAL
PURSUANT TO 37 CFR § 1.192**

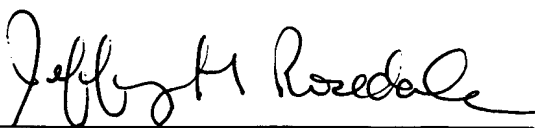
Transmitted herewith in triplicate is the REVISED APPEAL BRIEF in this application with respect to the Notice of Appeal received by The United States Patent and Trademark Office on **November 17, 2003** and the Appeal Brief filed **January 13, 2004**.

- ☐ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27 .
- ☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as:
- ☐ an Independent Inventor
 - ☐ a Small Business Concern
 - ☐ a Nonprofit Organization.
- ☐ Petition is hereby made under 37 CFR § 1.136(a) (fees: 37 CFR § 1.17(a)(1)-(4) to extend the time for response to the Office Action of _____ to and through _____ comprising an extension of the shortened statutory period of _____ month(s).

	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	FEE	RATE	FEE
<input type="checkbox"/> APPEAL BRIEF FEE	\$165	\$	\$330	\$
<input type="checkbox"/> ONE MONTH EXTENSION OF TIME	\$55	\$	\$110	\$
<input type="checkbox"/> TWO MONTH EXTENSION OF TIME	\$210	\$	\$420	\$
<input type="checkbox"/> THREE MONTH EXTENSION OF TIME	\$475	\$	\$950	\$
<input type="checkbox"/> FOUR MONTH EXTENSION OF TIME	\$740	\$	\$1480	\$
<input type="checkbox"/> FIVE MONTH EXTENSION OF TIME	\$1005	\$	\$2010	\$
<input type="checkbox"/> LESS ANY EXTENSION FEE ALREADY PAID	minus	(\$)	minus	(\$)
TOTAL FEE DUE		\$0		\$0

- ☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.
- ☒ The Appeal Brief Fee has already been paid on January 13, 2004.
- ☐ Please charge Deposit Account No. 23-3050 in the amount of \$.00. This sheet is attached in duplicate.
- ☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

Date: May 5, 2004


 Jeffrey H. Rosedale
 Registration No. 46,018

Woodcock Washburn LLP
 One Liberty Place - 46th Floor
 Philadelphia PA 19103
 Telephone: (215) 568-3100
 Facsimile: (215) 568-3439



DOCKET NO.: ISIS-4943

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Phillip Dan Cook
and Andrew Kawasaki**

Confirmation No.: **3783**

Serial No.: **09/996,263**

Group Art Unit: **1635**

Filing Date: **November 28, 2001**

Examiner: **James Schultz**

For: **SUGAR MODIFIED OLIGONUCLEOTIDES**

EXPRESS MAIL LABEL NO.: **EL 998516802 US**
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APPELLANT'S REVISED BRIEF PURSUANT TO 37 C.F.R. § 1.192

Appellants submit that their original brief dated January 13, 2004 complied with all applicable requirements. Nonetheless, in the interest of advancing prosecution, they submit this revised brief in response to the Notice of alleged non-compliance mailed on April 7, 2004. This brief is being filed in support of Appellant's appeal from the rejections of claims 8-13 in the Office Action dated August 12, 2003. A Notice of Appeal was filed on November 12, 2003 and received at the Patent Office on November 17, 2003.

1. REAL PARTY IN INTEREST

Based on information supplied by Applicants and to the best of the undersigned's knowledge, the real party in interest in the above-identified patent application is ISIS Pharmaceuticals, Inc., a corporation of Delaware, which is the assignee of Phillip Dan Cook and Andrew Kawasaki.

2. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Applicants, Applicants' legal representative, or the assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

3. STATUS OF CLAIMS

Claims 8-13 are pending in this patent application and are the subject of this Appeal. Claims 8-13 appear in Appendix A.

4. STATUS OF AMENDMENTS

On October 14, 2003, Applicants filed an amendment under 37 C.F.R. 1.116 to amend claim 8. The Advisory Action dated October 31, 2003, indicated that the amendment was entered. No further amendments have been filed.

5. SUMMARY OF INVENTION

The compositions useful for modulating the activity of an RNA or DNA molecule in accordance with this invention generally comprise a sugar-modified oligonucleotide which is hybridizable with a preselected nucleotide sequence of a target RNA or DNA molecule. It is generally desirable to select a sequence of DNA or RNA that is involved in the production of a protein whose synthesis is ultimately to be modulated or inhibited in its entirety (*see e.g.*, Specification at page 9, lines 4-13). Oligonucleotides suited for the practice of the present inventions generally comprise more than one 2'-modified nucleotide wherein the 2'-modifications are with different substituents (*see e.g.*, Specification at page 10, line 27 to page 11, line 4).

6. ISSUES

A. Whether or not the Examiner has refuted the evidence of record demonstrating that the specification and claims as originally filed convey to those skilled in the art that Applicants were in possession of the subject matter of claims 8-13 by at least the filing date of the instant patent application.

B. Whether or not the Examiner has refuted the evidence of record demonstrating that the specification and claims of Applicants' priority application (the "932 Application")

convey to those skilled in the art that Applicants were in possession of the subject matter of claims 8-13 by at least the 932 Application's filing date.¹

7. GROUPING OF CLAIMS

Applicants believe that claims 8-13 stand or fall together.

8. ARGUMENT

A. Applicants Were In Possession Of The Subject Matter

Although the Examiner rejected claims 8-13 under 35 U.S.C. §§112 and 102(b) due to an alleged lack of adequate written description for the claimed subject matter, he has failed to come forward with argument or evidence supporting this allegation and, notably, has failed to refute evidence of record to the contrary.

In rejecting a claim for lack of written description, the examiner carries the burden of establishing a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed (*see* MPEP §2163.04). In considering applicant's response to a rejection alleging lack of written description, the examiner is required to review the record as a whole, including amendments, arguments and any evidence submitted by applicant (*see id.*). If the rejection is maintained in spite of applicant's submission, any affidavits must be thoroughly analyzed and discussed in the subsequent Office Action (*see id.*).

The Examiner clearly did not satisfy these requirements with respect to the instant rejection. In rejecting claims 8-13 for alleged lack of adequate written description, the Examiner made a conclusory assertion that neither the application as filed nor the 932 Application provide anything that "would persuade one of skill in the art that applicant was in possession of" any oligonucleotides other than those whose synthesis is explicitly described (Office Action dated August 12, 2003, at page 4). In spite of the Examiner's failure to establish that the claims lack adequate written description in the application as filed and the

¹ As further discussed below, Applicants' claim of priority would obviate the rejection of claims 8-13 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,612,215 to Draper, *et al.* (the "Draper patent") because the filing date of the 932 Application is earlier than the earliest effective filing date of the Draper patent.

932 Application, Applicants submitted the declaration of Dr. Sidney M. Hecht, a person of skill in the art at all relevant times. Dr. Hecht's declaration establishes that those skilled in the art, upon review of the present application and the 932 Application, would have recognized from either document that Applicants were in possession of the claimed subject matter. In fact, Dr. Hecht refutes both of the unsupported assertions upon which the Examiner based his rejections.

With respect to support for the claims in the instant patent application, Dr. Hecht establishes that one of skill in the art having read the specification of the present application would acknowledge that the inventors had possession of the subject matter of claims 8-13 (Hecht Dec. ¶9). Specifically, the disclosure in the present application of the oligonucleotide of Example 13 having more than one different 2'-modification coupled with the disclosure of other possible 2'-modifications as set forth on page 10 of the specification lead to the conclusion that the specification and examples taken as a whole teach one skilled in the art to produce an oligonucleotide with more than one different 2'-modification and that the 2'-modifications can be selected from halo, azido, amino, alkoxy, thioalkoxy, alkylamino and alkyl (*id.*)

With respect to support for the claims in the 932 Application, Dr. Hecht establishes that the specification of the 932 Application,² taken as a whole, provides written description sufficient to support the full breadth and scope of the claimed oligonucleotides as of the 1992 filing date of the 932 Application (Hecht Dec. ¶13). The 932 Application discloses an example of an oligonucleotide having both 2'-methylthio and 2'-O-methyl substituents as well as oligonucleotides having one or more modified 2'-deoxy ribofuranosyl moieties wherein the modifications are selected from those recited in claims 8-13 (Hecht Dec. ¶¶11-13). In view of these disclosures, Applicants had possession of the claimed subject matter as of the 1992 filing date of the 932 Application.

In spite of Dr. Hecht's declaration testimony, the Examiner maintained his rejections in an Advisory Action, but did not identify any evidence refuting or otherwise calling such testimony into question. Contrary to the obligations imposed by the MPEP, the Examiner failed to analyze or substantively discuss, much less refute, Dr. Hecht's testimony. Rather, the Examiner simply indicated that Applicants' reply and Dr. Hecht's declaration were "not considered convincing" and that the arguments contained therein had somehow been

² The 932 Application issued as U.S. Patent No. 5,670,633. Dr. Hecht refers to the latter in discussing the disclosure that is common to both. (*See* Hecht Dec. ¶4)

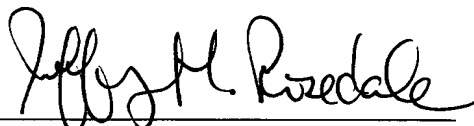
“addressed in full” in an earlier-issued Office Action (Advisory Action dated October 31, 2003, page 3). The Examiner, however, could not properly maintain his rejection without identifying contrary evidence or at least identifying some deficiency in Dr. Hecht’s testimony (*see* MPEP § 2163.04).

Because the unrefuted evidence of record demonstrates that both Applicants’ specification and the 932 Application provide more than adequate written description of the subject matter of claims 8-13, Applicants request that the rejection under 35 U.S.C. § 112, first paragraph, be reversed.

B. Applicants Are Entitled To The Filing Date Of the 932 Application

For the reasons stated above, Applicants’ specification and the 932 Application provide more than adequate written description of the subject matter of claims 8-13. Thus, Applicants are entitled to the filing date of the 932 application. Because the filing date of the 932 Application is earlier than the earliest effective filing date of U.S. Patent No. 5,612,215 to Draper, *et al.* (the “Draper patent”), Applicants request that the rejection of claims 8-13 under 35 U.S.C. §102(b) as allegedly being anticipated by the Draper patent be reversed.

Date: May 5, 2004



Jeffrey H. Rosedale
Registration No. 46,018

Joseph Lucci
Registration No. 33,307

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439



DOCKET NO.: ISIS-4943

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Confirmation No.: **3783**

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APPENDIX A TO APPELLANT'S BRIEF

The foregoing constitutes a complete listing of the claims on appeal.

Claims 1-7 (Canceled).

8 (Previously presented). A mixed sequence oligonucleotide or oligonucleotide analog including more than one 2'-modified 2'-deoxyfuranosyl moiety wherein said modification comprises substitution by halo, azido, amino, alkoxy, thioalkoxy, alkylamino, or alkyl, and wherein one of said 2'-modified 2'-deoxyfuranosyl moieties is different from another of said 2'-modified 2'-deoxyfuranosyl moieties.

9 (Previously presented). The mixed sequence oligonucleotide or oligonucleotide analog of claim 8, wherein one of said 2'-modified 2'-deoxyfuranosyl moieties comprises

substitution by halo, azido, amino, thioalkoxy, alkylamino or alkyl and another of said 2'-modified 2'-deoxyfuranosyl moieties comprises substitution by alkyloxy.

10 (Previously presented). The mixed sequence oligonucleotide or oligonucleotide analog of claim 8, wherein one of said 2'-modified 2'-deoxyfuranosyl moieties comprises substitution by halo, azido, amino, thioalkoxy or alkyl and another of said 2'-modified 2'-deoxyfuranosyl moieties comprises substitution by methoxy.

11 (Previously presented). The mixed sequence oligonucleotide or oligonucleotide analog of claim 8, wherein alkyl comprises a straight or branched chain alkyl.

12 (Previously presented). The mixed sequence oligonucleotide or oligonucleotide analog of claim 11, wherein alkyl includes unsaturation within the alkyl carbon chain.

13 (Previously presented). The mixed sequence oligonucleotide of claim 8 wherein said oligonucleotide is a nuclease resistant oligonucleotide.